REMARKS

Reconsideration of this application is respectfully requested. Claims 278-453 were previously pending in this application. Claims 278-309 and 373-404 have been canceled hereinabove. Claim 406 has been amended. Accordingly, claims 310-372 and 405-453 are presented for further examination on the merits.

In a sincere effort to narrow the issues and thereby expedite prosecution of this case. Applicants have canceled all claims directed to the phosphate-moiety labeled nucleotide. The canceled claims include claims 278-309 and 373-404. Among the canceled claims are claims 302-307 and 395-400 which were directed to either an oligo- or polynucleotide (in the case of claims 302 and 395) or a composition (in the case of claims 303-307 and 396-400). The latter sets of claims were dropped in order to avoid a rejection for improper dependent form due to the base claims having themselves been canceled.

A minor error in claim 406 has been corrected. There, the word "nucleotide" has been changed to – oligo- or polynucleotide – to conform the preamble of the claim with that recited in the base claim 405.

Finally, the title of the invention has been changed to conform with the subject matter now being claimed in light of the claim cancellations above, that is to say, "Oligo- or Polynucleotides, and Other Compositions Comprising Phosphate Moiety Labeled Nucleotides."

Acknowledgement is made of the fact that the Art Unit location of this application in the PTO has changed. Applicants and their attorney will direct all further correspondence to Group Art Unit 1807, Examiner Scott Houtteman.

The Rejection Under 35 U.S.C. §112, First Paragraph

Claims 278-453 stand rejected for allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the January 6, 1998 Office Action (pages 2-5), the Examiner stated:

> Newly submitted claims 278-453 are drawn to nucleotides, polynucleotides, etc. and compositions containing these products. Descriptive support was not pointed out, nor was it found for numerous limitations.
>
> Sig moiety is newly limited to "at least three carbon atoms having the "Sig" moiety. The points of attachment are limited in claims that newly recite chemical structures (for example claims 373, 405 and 433). Specific "Sigs" which attached to are attached to the phosphate are newly identified, for example, a glycosidic linkage moiety, biotin, iminobiotin, ferritin, an antigen, a hapten, an antibody, specific. Finally, the phosphate moiety has been newly limited to "a di-phosphate or a tri-phosphate moiety."
>
> [sic] sites of attachment, specific types of chemical linkages and that "sig" be "at least three carbon atoms," etc.
>
> The only support in the original disclosure was in a passage on pages 96-97 which begins "By way of summary" and nine other clauses pointed out in Applicant's response filed 11/24/97, pages 39-40.
>
> These passages define the attachment of "Sig" to the phosphate in generic terms. Sig is "covalently attached" to either base, sugar or phosphate. However, there is no *explicit* description of the various claimed products bound to the phosphate anywhere in the specification.
>
> In contrast, the base-linked "Sig" moieties have numerous complex chemical reactions which are necessary to synthesis the various products. These reactions include various solvents, reactants and protecting groups which are necessary so that only the base was modified and not the reactive groups on the sugar or phosphates. Thus, an explicit description of the "phosphate-Sig" reactions would have been expected in order for a skilled artisan to have reasonably concluded that the original disclosure evidenced "possession" of the currently claimed invention.
>
> Thus, in view of the generic disclosure and the absence of any specific "phosphate-Sig" reactions; and in view of the complex nature of reactions of labels to DNA, the skilled artisan would not have reasonably expected this specification to put the artisan in possession of the invention as now claimed.
>
> Since support for these claims was not found where pointed out nor elsewhere in the specification, these claims are considered "new matter."

Applicant argues, briefly, support is in various paragraph and clauses within the spec. This argument is not persuasive. These portions of the specification are merely generic recitations not support for the specific claim limitations.

Applicant argues that, according to the Engelhardt declaration filed 11/24/97, Example V and Halloran reference provide support. This argument is not persuasive. These methods do not mention DNA labeled at the phosphate moiety and thus do not provide a written description of the claimed invention.

Applicant further argues, briefly, that 16 references describing reactions to phosphorous, oxygen and coupling nucleic acids to other polymers provide support. This argument is not persuasive. These references do not describe the specific products in the claims but merely describe reactions that can be used to synthesize the claimed products if used on DNA. However, the reactions are used on other reactants in the references.

Applicant argues, briefly, that modifications of phosphate, sugar and base moieties are "functional equivalents;" that the reactions described for the base moiety are applicable to the sugar and phosphate moiety as well and that these reactions "were known in the art for modifying the phosphate moiety of a nucleotide.

These arguments are not persuasive. The standard for written description is not merely that one can find the limitations in the prior art or that the limitations are well known. The standard is that the specification must reasonably convey that the inventor had possession of the specific claimed invention. The limitations of the prior art can only be evidence of "possession" if they must necessarily be a part of the current specification. No portion of the specification was pointed out which is necessarily linked to any of the given prior art teachings.

The rejection for inadequate description is respectfully traversed.

It is respectfully submitted that the specification describes the subject matter now being claimed as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time this application was first filed in 1982. For the purpose of brevity, Applicants incorporate by reference herein the Declaration of Dr. Dean L. Engelhardt that was submitted with their November 24, 1997 Amendment Under 37 C.F.R. §1.116, together with their comments found in the Amendment, beginning on page 38, third paragraph, and continuing through page 44, first full paragraph.

For the Examiner's convenience and review, Applicants intend to supplement this response by submitting a table showing support for the present claims at hand, claims 310-372 and 405-453.

Applicants and their attorney acknowledge, with appreciation, the detailed analysis given by the Examiner in the portion of the instant Office Action quoted above. Notwithstanding its details, however, the analysis simply overlooks several tenets expostulated by the courts in setting up and applying the legal standards for adequate description and new matter.

First, the legal test for determining compliance with the written description requirement is whether the disclosure of an application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter. See, for example, Ex parte Parks, 30 USPQ 2d 1234 (Bd. Pat. App. & Int'f 1994). See also Ex parte Rohrer, 20 USPQ 2d 1460 (Bd. Pat. App. & Int'f 1991); Ex parte Holt, 19 USPQ 2d 1211 (Bd. Pat. App. & Int'f 1991); and Ex parte Remark, 15 USPQ 2d 1498 (Bd. Pat. App. & Int'f 1990).

Second, as stated by the Board of Patent Appeals & Interferences, "the examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in [the] specification disclosure a description of the invention defined by the claims. Ex parte Parks, *supra* at 1236.

Third, it is not necessary that the claimed subject matter be described identically, but the disclosure originally filed must reasonably convey to those skilled in the art that the applicant invented the subject matter later claimed. Ex parte Rodgers, 27 USPQ 2d 1738 (Bd. Pat. App. & Int'f 1992). Moreover, it not even necessary that the claimed subject matter be described in *ipsis verbis* or *haec verba* to satisfy the written description requirement of 35 U.S.C. §112. Nelson v. Bowler, 1 USPQ 2d 2076 (Bd. Pat. App. & Int'f 1986); and Staehelin v. Secher, 24 USPQ 2d 1513 (Bd. Pat. App. & Int'f 1992).

Fourth, it is not necessary for the applicant to reveal a conscious appreciation on the part of the applicant of the significance of the limitation in question. The written description requirement can be satisfied by showing that the disclosed subject matter, when given its "necessary and only reasonable construction," inherently (i.e., necessarily) satisfies the limitation in question. Behr v. Talbott, 27 USPQ 2d 1401 (Bd. Pat. App. & Int'f 1992).

Fifth and finally, the basic test of whether the prior disclosure reasonably conveys to those skilled in the art that the applicant had possession of the later claimed subject matter at the time of the earlier disclosure requires specific reference to the knowledge of those skilled in the relevant art [in this instance, the biotechnology arts]. Vas-Cath, Inc. v. Mahurkar, 935 F. 2d 1555, 19 USPQ 2d 1111 (Fed. Cir. 1991).

The instant rejection can be pared down to a simple inquiry: Does the original specification reasonably convey to the skilled artisan that Applicants had possession of the subject matter of the claims at hand (310-372 an d 405-453) at the time this application was first filed on June 23, 1982? Or, to put it in negative terms, what is lacking in the original specification that would prevent the possession of the claimed subject matter from being reasonably conveyed to the skilled artisan?

It is respectfully submitted that the instant disclosure passes muster under any or all of the foregoing legal pronouncements on adequate description. In Dr. Engelhardt's Declaration submitted with their November 24, 1997 Amendment, Applicants pointed to almost a dozen instances of support for their claimed subject matter.[1] [2] Despite those numerous instances which have been acknowledged in

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[1] Listed on pages 39 & 40 of Applicants' November 24, 1997 Amendment as well as on pages 10 & 11 of Dr. Engelhardt's Declaration, these almost dozen or so instances of support include the following:

page 90, last paragraph	. . . and a signalling chemical moiety Sig covalently attached thereto, either to the P, S or B moiety.
page 93, first paragraph	. . . include a chemical moiety Sig covalently attached to the P, S and/or B moieties.
page 96, first paragraph	. . . by having covalently attached thereto, to the P moiety and/or the S moiety and/or the B moiety, a chemical moiety Sig.
page 98, first paragraph	. . . the Sig component or chemical moiety of nucleotides of this invention can be directly covalently attached to the P, S or B moieties or attached thereto via a chemical linkage or linkage arm . . .
page 103, first full paragraph	. . . and the signalling or self-detecting moiety, Sig, covalently attached to either the P, S or B moieties, as indicated hereinabove, . . .
page 104, first paragraph	. . . nucleotides in accordance with this invention containing the above-described components P, S, B and Sig, . . .
page 105, first paragraph	. . . the nucleotides of this invention include the P, S, B and Sig components wherein the Sig is covalently attached to either the P, S or B moieties

the instant Office Action, a written description for the claims at hand has been found wanting on the basis that "there is no *explicit* description of the various claimed products bound to the phosphate anywhere in the specification" or "an explicit description of the 'phosphate-Sig' reactions." But the requirement for an *explicit* description of the claimed subject matter is *not* a prong of any legal test for adequate written description.

Perhaps the most telling pronouncement on this subject is the aforementioned Ex parte Parks case, a copy of which is attached as Exhibit 1. In that case involving a reissue application for method claims, the examiner had contended that the rejected claims lacked adequate descriptive support because there is "no literal basis for the" claim limitation "in the absence of a catalyst." The Board of Patent Appeals & Interferences remarked at the outset:

> Clearly, the observation of a lack of literal support does not, in and of itself, establish a *prima facie* case for lack of adequate descriptive support under the first paragraph of 35 U.S.C. §112. *In re Herschler, supra*; *In re Edwards, supra*; *In re Wertheim, supra*.

Furthermore, in the Parks case, the Board noted that:

> Moreover, according to two declarations by Wentworth, a professor of chemistry at the University of Houston, whose expertise in this particular art has not been challenged, one having ordinary skill in the art would have recognized that the reaction generating nitric oxide, according to the equation disclosed in the '562 patent, is conducted without a catalyst. See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555,

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page 105, second paragraph The moiety Sig attached to the special nucleotides of this invention containing the other moieties or components P, S, B provides a site per se for the attachment thereto, the Sig component, . . .

page 106, first paragraph . . . the special P, S, B and Sig-containing nucleotides of this invention, . . .

Other instances of support include Example V in the specification, and originally filed claims 141 and 143, all of which are referred to in Applicants' November 24, 1997 Amendment, or Dr. Engelhardt's Declaration, or both.

[2] Because the nucleotide claims have been dropped by the present Amendment, Applicants note that other claims among the originally filed claims were directed to polynucleotides comprising one or more modified nucleotides, including one or more phosphate modified nucleotides. Such originally filed claims include claim 146 ("A single-stranded polynucleotide comprising one or more nucleotides in accordance with Claim 143."), claim 147 ("A double-stranded polynucleotide comprising one or more nucleotides in accordance with Claim 143."), claim 148 ("A single-stranded polydeoxyribonucleotide containing at least 12 nucleotides and comprising one or more nucleotides in accordance with Claim 143."), and claim 151 ("A polynucleotide comprising at least one nucleotide in accordance with Claim 143.").

> 19 USPQ 1111 (Fed. Cir. 1991); *In re Lemin*, 364 F.2d 864, 150 USPQ 546 (CCPA 1966). Thus, it cannot be said that the originally filed disclosure would not have conveyed to one having ordinary skill in the art the concept of effecting decomposition at an elevated temperature in the absence of a catalyst. *In re Anderson, supra.*

And the use of a declaration or affidavit to overcome a new matter rejection under the first paragraph of 35 U.S.C. §112 has not been limited to the Parks case. In the case of In re Oda [443 F.2d 1200, 170 USPQ 268 (C.C.P.A. 1971), the applicant successfully submitted an affidavit to overcome a written description rejection that stemmed from the mistranslation of the words "nitric acid" to "nitrous acid" from the priority Japanese patent application on which the U.S. application was based.

In the rejection at hand, Applicants have enumerated specific instances of support both through their previous responses and Dr. Engelhardt's Declaration. In his Declaration, Dr. Engelhardt has indicated that the specification as originally filed in 1982 reasonably conveys that the coinventors were in possession of the subject matter now being claimed. Under the law, and in particular, under the Ex parte Parks case, *supra*, it cannot be said that the originally filed disclosure would not have conveyed to one having ordinary skill in the art the instantly claimed oligo- or polynucleotides and other compositions comprising phosphate moiety labeled nucleotides. In fact, Applicants have clearly established that their disclosure amply supports the subject matter of claims 310-372 and 405-453 as required under the first paragraph of 35 U.S.C. §112.

In view of their earlier remarks in previous responses including their November 24, 1997 Amendment, Dr. Engelhardt's Declaration and the foregoing comments, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

The Objection and Rejection Under 35 U.S.C. §112, First Paragraph

Claims 278-453 stand rejected for nonenablement under 35 U.S.C. §112, first paragraph. In the Office Action (pages 5-6) the Examiner stated:

Claims 278-453 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not disclosed in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 278-453 are broadly drawn to nucleotides having various "Sig moieties" attached to the phosphate moiety.

The specification contains a sufficiently detailed disclosure, such as in Examples I-VII, to enable the construction of "sig-base" nucleotides, that is nucleotides in which the "Sig" moiety is linked to the base. It is noted that these reactions contain many specific solvents, reactants and protecting groups. This detailed disclosure enables one to obtain a reasonable product yield, a product of suitable stability for it's intended use in nucleic acid detection assays and a product reasonably free of unwanted side products in which the Sig moiety is attached at the wrong places on the nucleotide.

However, there is no analogous disclosure for the attachment of the "Sig-phosphate" nucleotides. The broadly claimed "Sig moieties" include a very diverse population of molecules, from simple inorganic compounds like radioactive Cobalt to the complex organic molecules like enzymes. Accordingly, there are a vast number of possible chemical reaction schemes one could attempt. Without specific guidance or examples, the skilled artisan would expect that the vast majority of these reaction schemes would fail. Either the product yields would be low, the products would be too unstable or the products would be too hard to purify away from extraneous side products.

It is difficult to predict the behavior of a complex organic molecule with numerous functional groups: primary amines, carboxyl groups and alcohol groups. There is no way to establish, before the fact, which reaction conditions will result in high yields and stable products that can be purified from extraneous byproducts.

The level of skill is high in this field. Nevertheless, in view of the large scope of these claims, the lack of any guidance or specific examples, the high degree of unpredictability, the complex nature of the invention which requires both inorganic and organic chemical syntheses; it would have required undue experimentation to enable a reasonable number of embodiments within the scope of these claims.

Applicant argues, briefly, that only minimal experimentation was required to practice the claimed invention in view of 16 references which teach relevant reactions. This argument is not persuasive. It is undue experimentation to expect the skilled artisan (1) to search out and find the references and (2) know which references to use. It is important to note that none of the references are specifically drawn to synthesis of the claimed products.

The enablement rejection is respectfully traversed.

It is respectfully submitted that the instant specification provides a sufficiently enabling disclosure for the practice of the presently claimed invention. Again, for the purpose of brevity, Applicants incorporate by reference herein the

Declaration of Dr. Dean L. Engelhardt that was submitted with their November 24, 1997 Amendment, together with their comments found on pages 45-46 in their Amendment.

Applicants sincerely believe that a proper application of the statutory standard for enablement leads inevitably to the conclusion that their original disclosure would have enabled the skilled person in the art to practice their claimed invention at the time this application was first filed in 1982.

While judging and concluding the specification to contain a sufficiently detailed disclosure for constructing the "Sig-BASE" nucleotides, the instant objection and rejection nevertheless finds no analogous disclosure for the "Sig-Phosphate" nucleotides. Applicants respectfully disagree for the reasons set forth below and in their November 24, 1997 Amendment as supported by Dr. Engelhardt's Declaration. These reasons include, among others, Example V on page 57 in the specification. That example describes a method for attaching biotin, one of the embodiments for Sig, to the phosphate moiety of a mononucleotide and an oligonucleotide that are coupled to a protein, poly-L-lysine. Using the procedure detailed in Example V, the biotinylated poly-L-lysine is coupled to a terminal oxygen of the phosphate moiety or to a terminal phosphorus.

Applicants contend that the parameters and factors governing or controlling the "Sig-BASE" nucleotides are of no greater or lesser consequence than those affecting the "Sig-Phosphate" nucleotides. Armed with the specification (including Example V) and the description in the specification of the various Sig embodiments, together with the knowledge in the art, the skilled artisan could readily practice, without undue experimentation, the instantly claimed invention in the form of oligo- or polynucleotides and other compositions comprising phosphate-moiety labeled nucleotides. In many respects, labeling the phosphate moiety is conceptually an easier task than labeling a purine or a deazapurine or a pyrimidine base. Each of the latter contains several potential labeling positions and substituents that could effect yields, stability and purification. With the phosphate moiety, the skilled artisan is dealing with modifications affecting only two kinds of atoms, the phosphorus and the oxygen atoms.

Moreover, chemistry involving phosphate modification was well developed by the time this application was originally filed in June 1982. In fact, Dr. Engelhardt's Declaration points to no less than three scientific publications disclosing modifications to the oxygen atom(s) of the phosphate moiety, and no less than eight scientific publications for modifications to the phosphorus atom. These publications are by no means an exhaustive listing of literature in the art. In fact, Applicants have every reason to believe that the number of publications disclosing phosphate chemistry runs far greater than those submitted in Dr. Engelhardt's Declaration. As expounded by the Federal Circuit and retold in Irah Donner's treatise Patent Practice: Practice & Procedure Before the U.S. Patent Office [BNA, Washington, D.C., 1996, Chapter 8, "Disclosure Under 35 U.S.C. Section 112, First Paragraph, page 457], specifications

> need only be reasonable with respect to the art involved; they need not inform the layman nor disclose what the skilled already possess. **They need not describe the conventional . . . The intricacies need not be detailed ad absurdum.** [bold added]

[citing General Elec. Co. v. Brenner, 407 F.2d 1258, 159 USPQ 335, 337 (D.C. Cir. 1968) (citing Loom Co. v. Higgins, 105 U.S. (15 Otto) 580 (1882).

The courts have also stated on several occasions:

> The question is whether the disclosure is sufficient to enable those skilled in the art to practice the claimed invention, hence **the specification need not disclose what is well known in the art.** [bold added]

[citing Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co., 730 F.2d 1452, 221 USPQ 481, 489 (Fed. Cir. 1984) (citing In re Myers, 410 F.2d 420, 161 USPQ 668 (C.C.P.A. 1969. *See also* Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 1534, 3 USPQ 2d 1737, 1743 (Fed. Cir.) ("A patent need not teach, and preferably omits, what is well known in the art.), *cert. Denied*, 484 U.S. 954 (1987)]

Under the foregoing legal principles, the specification in and of itself provides an enabling disclosure for Applicants' claimed compositions.

Beyond that, Applicants respectfully maintain that Dr. Engelhardt's Declaration has established that the specification is enabling because any other information for practicing the invention at hand was conventionally known and available in the art. In this regard, the long-established general rule is that

> An applicant must show that **anyone skilled in the art would have actually possessed the required information or would reasonably have been able to locate the information with no more than reasonable diligence.** [bold added]

[In re Haworth, 654 F.2d 103, 210 USPQ 689, 692-93 (C.C.P.A. 1981) (citing In re Lange, 644 F.2d 856, 863, 209 USPQ 288, 294 (C.C.P.A. 1981)].

In view of the foregoing remarks, including previous submissions, and the established legal principles set forth above, Applicants respectfully request reconsideration and withdrawal of the enablement objection and rejection.

The Rejection Under 35 U.S.C. §103

Claims 278-453 stand rejected under 35 U.S.C. §103 for being unpatentable over Gohlke et al., U.S. Patent No. 4,378,458, filed on March 30, 1981 in view of Sodja et al., Nucleic Acids Research 5(2):385-401 (1978) and further in view of Applicants' admissions. In the Office Action (pages 7-9), the Examiner stated:

> Gohlke discloses, for example, col 3, lines 3-22, the use of detection assays using labels such as fluorescent compounds, chemiluminescent compounds and enzymes like β-galactosidase and, in col. 2, lines 32 and 35, antibodies.
>
> Sodja teaches on page 386 the attachment, to the free 3' OH end of RNA, an avidin-ferritin label using the lysine groups of the polypeptide cytochrome-c).
>
> It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the labels of Sodja in the methods of Gohlke for the expected benefit of using electron microscopic detection of the bound label.
>
> Applicant admits, in the amendment filed 11/24/97, on page 43, that "Numerous reactions were known in the art for modifying the phosphate moiety of a nucleotide" and "explicit description of such known reactions would not have been necessary." It would have been *prima facie* obvious to one of ordinary skill in the art at the time

the invention was made to use the "numerous reactions known in the art" for the expected advantage of labeling DNA.

Applicant argues that immunoassays are non-analogous to nucleic acid labeling assays. This argument is not persuasive. Many of the same labels were used in both assays, for example biotin. Also, Gohlke et al., a immunoassay publication is using a nucleotide.

Applicant argues that immunoassay modifications would not have been expected to function in nucleic acid technology because of the different "geometry" of the interactions between immunological products and the "two-dimensional" hybridization of nucleic acids. This argument is not persuasive. There is no evidence presented of the state of mind of scientists in immunology and nucleic acid hybridization. The merely conclusory statements of counsel on this important an speculative matter carry little weight.

Applicant argues that because of the reaction scheme, Sodja breaks open the sugar ring of the nucleotide and are "not remotely connected to the invention at hand." First, the claims are not limited to either an open sugar ring or a closed sugar ring. The claims merely recite "a sugar moiety."

Second, since the modified nucleic acid can still be used in a hybridization assay it is unclear why the state of the sugar moiety on the terminal base of a nucleotide would be at all critical to the invention. Thus, either an open or closed sugar ring are art recognized alternatives. The ordinary artisan would have expected either to work in a nucleic acid hybridization assay.

Third, applicant admits that "Numerous reactions were known in the art for modifying the phosphate moiety of a nucleotide." (See the 16 references on pages 45 and 46 of the Amendment filed 11/24/97. Thus, to the extent that an open ring would be a disadvantage, the ordinary artisan would be motivated to use any of these "numerous reactions."

The obviousness rejection is respectfully traversed.

In order to sustain a rejection a *prima facie* obviousness rejection, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination or other modification. In the rejection at hand, it is respectfully submitted that the teachings in the cited Gohlke and Sodja documents are not sufficient for the ordinarily skilled artisan to have made the requisite modifications that would have been necessary to arrive at the presently claimed invention.

As noted in the opening remarks of this Amendment, the present claims are directed solely to oligo- or polynucleotides and other compositions comprising at least one phosphate moiety labeled nucleotide that is capable both of non-

radioactive detection and incorporation into an oligo- or polynucleotide or such other composition. Phosphate moiety labeled nucleotides are no longer being pursued, having been altogether canceled by this Amendment. An examination of Gohlke's patent and Sodja's paper clearly shows that neither document teaches nor suggests the instantly claimed compositions.

The gist of the instant rejection is that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the labels of Sodja in the methods of Gohlke for the expected benefit of using electron microscopic detection of the bound label. As explained in greater detail below, a person of ordinary skill in the art could not have combined Sodja's labeling chemistry with Gohlke's methods, particularly because the latter's substrate could not be incorporated or polymerized into Applicants' instantly claimed compositions. Even if such a person did combine both disclosures (and motivation to do so was entirely lacking), he or she would not have arrived at the instant invention because of severe irreconciliable deficiencies in the respective disclosures.

First, Gohlke's disclosed substrate cannot be polymerized or incorporated into the instantly claimed oligo- or polynucleotide or composition. At best, Gohlke et al. discloses what could liberally be described as a hydrolase substrate contemplated for use as an enzyme (ribonuclease) substrate. Gohlke's substrate has no phosphate at the 5′ position of the sugar, and it has only a single phosphate ester at the 3′ sugar position. And that latter phosphate ester is blocked by the nature of the ester bond itself and by virtue of the bulky substituents esterified thereto. Because the 3′ position in their substrate (and the 3′ or 5′ position in their intermediates) is always blocked, Gohlke's substrate cannot in any way be polymerized or incorporated into an oligo- or polynucleotide, or other polymeric composition as set forth the present claims. Thus, neither Gohlke's final substrate product nor any of his intermediates in his disclosure can be incorporated – either enzymatically or chemically – into the instant compositions.

Second, and contrary to the instant rejection, a person of ordinary skill in the art could not have used Sodja's labeling chemistry in Gohlke's disclosed substrate because the former requires the two 2′,3′-OH groups for their disclosed

periodate oxidation. In Gohlke's disclosure and as explained above, the 3' position of the sugar moiety is always blocked, and, therefore, is always unavailable for any such periodate oxidation. It is quite plain, therefore, that the ordinarily skilled artisan would not have looked to apply Sodja's labeling system that is premised on the periodate oxidation of the 2',3'-OH groups to Gohlke's methods and substrate which block the 3'-OH group. The chemistries in their respective disclosures are simply incompatible to the point of building total discouragement in one seeking to combine Gohlke and Sodja.

Third, even if a person of ordinary skill in the art would have attempted to applying Sodja's labels to Gohlke's methods (and clearly, it was impossible to do so), he or she clearly would not and could not have arrived at the instant invention. As explained in full detail above, Gohlke's disclosed substrate cannot be incorporated or otherwise polymerized into an oligo- or polynucleotide, or other composition. Therefore, even to attempt to apply Sodja's labeling chemistry to Gohlke's methods and substrate would still leave the ordinarily skilled artisan with Gohlke's composition that could not be incorporated into Applicants' instantly claimed compositions.

Fourth, with respect to Sodja's sugar ring opening chemistry, Applicants maintain that the resulting product is no longer a nucleotide. A nucleotide presupposes the presence of a cyclic sugar. For example, in his book Principles of Nucleic Acid Structure [Springer-Verlag, New York, 1984, Chapter 1, "Why Study Nucleotide and Nucleic Acid Structure?" page 1], Wolfram Saenger makes the following definition:

> A nucleotide consists of three molecular fragments: sugar, heterocycle, and phosphate. **The sugar, ribose or deoxyribose, is in a cyclic, furanoside form** and is connected by a β-glycosyl linkage with one of four heterocyclic bases to produce the four normal nucleosides: adenosine, guanosine, cytidine, and thymidine (uridine in ribonucleic acid, RNA). If the 3'- or 5'-hydroxyl group of sugar is phosphorylated, we have a nucleotide. This unit, the nucleotide, is not only the building block of the polynucleotides DNA and RNA but it also exhibits independent functions. [bold added]

For the Examiner's review, a copy of the above quotation from page 1 of Saenger's Principles of Nucleic Acid Structure is attached as Exhibit 2.

In The Biochemistry of Nucleic Acids [11th Edition, Chapman and Hall, Chapter 1, "The Structure of Nucleic Acids," 1992, page 6], Adams et al. describe the sugar component of nucleic acids thusly:

> **2.1.3 Pentose and deoxypentose sugars**
> The sugar component of RNA is D-ribose which in polynucleotides occurs in the **furanose form.** In DNA this sugar is replaced by 2-deoxyribose also in the D-**furanose form** (Fig. 2.6). . . [bold added]

A copy of pages 6-7 from Adams' eleventh edition The Biochemistry of Nucleic Acids is attached as Exhibit 3.

And, of course, "the bible of biochemistry," Lehninger's Principles of Biochemistry [Worth Publishers, Inc., New York, 1982, Chapter 27 "DNA: The Structure of Chromosomes and Genes," page 796] provides the following description:

> Two kinds of pentoses are found in nucleic acids. The recurring deoxyribonucleotide units of DNA contain *2'-deoxy-D-ribose*, and the ribonucleotide units of RNA contain *D-ribose*. **Both pentoses occur in nucleotides in their β-furanose forms.** [bold added]

A copy of page 796 from Lehninger's classic textbook is attached as Exhibit 4.

According to Stenesh [Dictionary of Biochemistry and Molecular Biology, 2nd edition, John Wiley & Sons, Inc., New York, 1989, page 188], a **furanose** is

> A monosaccharide having a five-membered **ring structure** [bold added].

A copy of page 188 from Stenesh's Dictionary is attached as Exhibit 5.

Because by definition, furanose is a monosaccharide having a five-membered ring structure, Applicants respectfully maintain that any chemistry or reaction that opens up the furanose, such as Sodja's periodate oxidative labeling chemistry, inevitably leads to a resulting structure that is not a nucleotide.

In closing, Applicants are reminded of the story of the country farmer who having been approached for directions by the urbane visitor driving the slick sports

car, laconically remarks "You can't get there from here." By the same token, it is believed that the two cited documents represent an impermissible and, moreover, an impossible route to reaching Applicants' claimed invention.

In view of the foregoing remarks and submitted exhibits, Applicants respectfully request reconsideration and withdrawal of the obviousness rejection, thereby placing each of the pending claims, 310-372 and 405-453, in allowable condition. An early indication as to their allowability is respectfully urged.

* * * * * * *

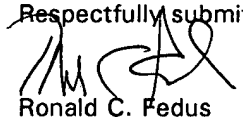
SUMMARY AND CONCLUSIONS

Claims 310-372 and 405-453 have been presented for further examination in this application. Only the title of the invention and a minor error in claim 406 have been amended.

No claim fee is deemed necessary in connection with the filing of this Amendment in which several claims, namely, 278-309 and 373-404, have been canceled. This Amendment is being accompanied by a Request For An Extension of Time (3 months) and authorization for the fee therefor. If any fee is due in connection with this Amendment or the extension request, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 05-1135.

If it would be helpful to expediting prosecution of this application, Applicants' undersigned attorney may be contacted during normal daytime business hours at (212) 583-0100, or by facsimile, at (212) 583-0150.

Respectfully submitted,



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